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(54) Title: GENITAL LUBRICANTS WITH ZINC TO REDUCE IRRITATION AND ALLERGIC REACTIONS

(57) Abstract

This invention discloses that certain types of zinc compounds, if added to formulations (such as condom lubricants and lubricant gels) that are applied topically to one or more genital surfaces during sexual intercourse, can reduce the irritation caused by spermicidal and/or microbicidal agents, which act essentially as toxins designed to kill various types of cells and microbes. Preferred zinc compounds include zinc lactate, zinc gluconate, zinc acetate, and other water–soluble organic zinc salts. In addition to reducing irritation caused by surfactants (such as nonoxynol or octoxynol) and other microbicides in topical genital formulations, zinc–containing additives can help stabilize and protect cellular membranes, thereby helping protect genital surfaces against damage caused by repeated exposure to agents that attack the lipid membranes that surround mammalian cells. Zinc–containing additives can also help accelerate the healing and closure of lesions or other skin breaches caused by spermicidal or microbicidal toxins, or by abrasion, rashes, sexually transmitted diseases, or other causes. Because of these effects, topical genital formulations containing spermicides or microbicides, and also containg a suitable zinc compound, can promote better skin tone and better genital health and hygiene, compared to similar formulations containing a spermicide and/or microbicide without zinc. In addition, zinc–containing additives can also reduce the risk and severity of allergic reactions to latex proteins in condoms.

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GENITAL LUBRICANTS WITH ZINC TO REDUCE IRRITATION AND ALLERGIC REACTIONS

RELATED APPLICATIONS

This application claims priority based on U.S. provisional patent applications serial numbers 60/053,162 and 60/053,110, both filed on July 18, 1997, and U.S. provisional patent applications serial numbers 60/069,710, _____ [Attorney docket ZN-SURF-1], and _____ [Attorney docket ZN-LTX-1], all filed on December 16, 1997. The teachings of these applications are incorporated herein by reference.

BACKGROUND OF THE INVENTION

This invention is in the field of condom lubricants and other genital lubricants and pharmaceuticals that are topically applied to genital surfaces, before or during sexual intercourse.

Recently, zinc salts in genital lubricants have been the subject of several US patents issued to Kelly (one of the co- inventors of this subject invention). Those US patents include 5,208,031 (May 1993); 5,482,053 (January 1996); 5,545,673 (August 1996); 5,599,551 (Feb. 1997); and 5,624,675 (April 1997). The teachings of those patents are incorporated herein by reference. However, those cited patents all relate to the use of zinc salts as anti-viral agents, and do not disclose or suggest the possibility that zinc might be able to reduce irritation caused by spermicides or microbicides, or that zinc can reduce the frequency and severity of allergic reactions to latex condoms.

Many condom lubricants, spermicidal contraceptives, and other "topical genital formulations" (defined in detail below) contain either or both of the following: (1) at least one "spermicide" (as used herein, this refers to any agent that kills sperm cells); and (2) at least one "microbicide" (as used herein, this refers to any agent that kills or blocks the replication of one or more types of microbes, including bacteria, viruses, fungus, protozoa, mycoplasma, and chlamydia). Some chemical agents such as surfactants (discussed below) have both spermicidal and microbicidal activity.

For convenience, the terms "toxin" and "toxic agent" are used identically and coextensively herein to refer to any agent (i) which is actually used in a topical genital formulation, and (ii) which is pharmacologically effective as a spermicide and/or microbicide. The term "toxin" is therefore used herein as a convenient, shorthand reference term for a specific group of substances, i.e., agents that function as spermicides and/or microbicides and that are contained in topical formulations used in connection with sexual intercourse, for purposes such as contraception and/or reducing the risk of infection by one or more sexually transmitted microbes.

One of the most important classes of toxins in topical genital formulations includes surfactants which act as contraceptives by killing sperm cells. The most widely used surfactant is called "nonoxynol", and the most commonly used form of this compound is called "nonoxynol-9" (often abbreviated as "N-9"). A similar agent called "octoxynol", containing fewer carbon atoms, is also used as a contraceptive, mainly in a specific form called "octoxynol-8". Their structures can vary somewhat; for example, nonoxynol-11 (which contains 11 -OCH2CH2- subunits in the hydrophilic portion of the molecule) also is used as a spermicidal surfactant, and still other versions of nonoxynol (such as N-15 and N-30, which are more soluble in water than N-9) are used for other purposes.

Surfactants such as nonoxynol also are used as spermicidal components in various gels and foams, including (i) "stand-alone" gels, which are packaged in a plastic tube or other watertight container, without a condom, for use either as a lubricant or for placement inside the cup of a diaphragm before it is inserted into a vagina; (ii) gels that are packaged in single-dose syringe-type tubular plastic applicators, for insertion deep into the vagina so that the entrance to the cervix will be blocked by the gel; and (iii) foams that are packaged in pressurized cans, for loading into a reusable plunger-type plastic applicator for insertion deep into the vagina.

The name "surfactant" was derived from the phrase, "surface active agent". The surfactants discussed herein are limited to spermicidal surfactants, as set forth below. Most of this class of surfactants comprises two-domain molecules that contain both (1) a water-soluble "hydrophilic" domain, which has a polar chemical structure that mixes readily with water molecules, which are also polar; and, (2) a hydrophobic (also called "lipophilic" or "oleophilic") domain, which does not mix readily with water, and which mixes instead with non-polar molecules in oil, grease, and fat. In both nonoxynol and octoxynol, the clustered carbon atoms form the oleophilic domain, while the other portion (which contains

numerous oxygen atoms) is the water-soluble domain.

When a two-domain surfactant is added to a mixture of oil and water, the nature of the surfactant molecules causes them to position themselves in the interfaces between the water and the oil. When a surfactant molecule reaches that position, it orients itself in a manner that causes the hydrophilic domain to extend into a water droplet, while the oleophilic domain extends into an oil droplet.

When this occurs, the surfactant disrupts the interface between the water and the oil, and it substantially reduces the "surface tension" between the two different components (also called the "phases" of the mixture). This increases the solubility of the oily compound in the water (and vice versa), and it causes droplets or globules to be broken apart into much smaller droplets or globules. This is why soap or detergent (which are also surfactants) can, in effect, break down and solubilize an oily layer or deposit on skin or on a metallic, plastic, or other surface, and why soap or detergent can help clean oily deposits off of such surfaces.

Many surfactants can also kill bacteria, at least some types of viruses, and other microbes, by disrupting, weakening, and breaking apart the membranes that surround and enclose the microbes, and possibly by attacking other microbial components. This is one reason soaps and detergents can act as disinfectants; in addition to removing oily deposits or films that might shelter microbes, they also help kill microbes directly.

This is a simplified explanation; more information on the chemistry and biological effects of surfactants, which are very widely used in condom lubricants and other genital lubricants and contraceptives, is available in numerous reference works known to those skilled in the art.

A wide variety of different surfactant agents are available, with a wide variety of surfactant potency. For example, industrial-strength soaps and detergents (used for cleaning metal and other non-living surfaces) have high levels of surfactant activity; by contrast, soaps and detergents that are intended to contact human skin are selected and formulated to have lower levels of surfactant potency, to avoid or minimize any skin irritation.

Nonoxynol and octoxynol are used as spermicides (i.e., as contraceptive agents which reduce the risk of pregnancy) because they have surfactant potency levels which render them useful for that particular purpose. For many people, they cause relatively low and tolerable levels of irritation, even when actively rubbed onto the tender and sensitive epidermis of exterior genitalia or into the often highly sensitive epithelial surfaces ("mucous

membranes") inside the urethra, vagina or rectum. However, despite relatively low levels of irritation to epidermal and epithelial membranes, nonoxynol and octoxynol are sufficiently aggressive in their surfactant activity to be effective in killing sperm cells, by disrupting and breaking apart the lipid bi-layer membranes that surround and enclose sperm cells.

Nonoxynol and octoxynol each cause noticeable irritation in a substantial portion of the population. Among some users, this irritation rises to the level of a genuinely unpleasant and distracting burning or tingling sensation; among others, it generates the sensation of a foreign, unnatural chemical presence. This type of irritation caused by nonoxynol and octoxynol is an important drawback which interferes with the type of consistent and reliable use (i.e., during each and every act of intercourse) that is optimal for preventing pregnancy.

Accordingly, efforts have been made by a number of researchers to identify various other agents that can be added to nonoxynol or octoxynol, to reduce the levels of irritation that the surfactants cause while still providing good spermicidal activity. Such efforts are described in, for example, Lee et al, J. Pharm. Sci. 85: 91-5 (1996), which describes the use of various chelating agents, such as ethylene-diamine-tetraacetic acid (EDTA), ethylene bis(oxy-ethylene-nitrilo)-tetraacetic acid, and gramicidin, in a polymeric carrier containing Carbopol 934P and nonoxynol; White et al, Contraception 52: 241-7 (1995), which discusses the use of propranolol to alter calcium uptake by sperm cells, in conjunction with nonoxynol; and Courtot et al, Human Reprod. 9: 1999-2005 (1994), which discusses the use of cholic acid and/or benzalkonium chloride, combined with nonoxynol.

It has been known for years that surfactants such as nonoxynol and octoxynol have certain types of anti-viral activity; they can inactivate certain types of viruses, rendering those viruses non-viable and non-infective. This type of anti-viral activity (often called "virucidal" activity, even though viruses aren't regarded as "alive" by most scientists) is most effective against viruses that are surrounded by lipid envelopes. Such viruses with lipid envelopes include several major types of sexually-transmitted viruses that can infect humans, including herpes simplex viruses (HSV), which cause genital herpes, and human immunodeficiency viruses (HIV), which cause AIDS.

Without intending to be bound by theory or limited to any specific cellular or biological mechanism of activity either here or elsewhere in this specification, the Inventors state that the virucidal activity of nonoxynol and octoxynol appears to involve at least some

of the same molecular mechanisms that cause surfactants to kill sperm cells. The surfactant molecules disrupt and break apart the lipid bi-layer membranes which surround sperm cells, and which also surround sexually transmitted viruses. Accordingly, many people use nonoxynol-lubricated condoms even when there is little or no risk of pregnancy, in the hope that the nonoxynol will help reduce the risk of becoming infected by AIDS or herpes.

However, several studies have directly contradicted and undercut the hope that nonoxynol and/or octoxynol can reduce the risk of contracting AIDS or genital herpes. Such studies are described in, for example, Kreiss et al, JAMA 268: 477-482 (1992), and Rowe, Lancet 349: 1074 (1997). These studies (most of which have focused on women) suggest that frequent use of nonoxynol can cause the formation of lesions inside the vagina. Such lesions can breach and disrupt the protective outer surfaces of the membranes inside the vagina, and apparently can lead to an increased (rather than reduced) risk of HIV infection.

Accordingly, the use of surfactants such as nonoxynol or octoxynol is not entirely satisfactory, since such surfactants suffer from at least three known limitations: (1) they cause irritation in some users; (2) they can damage and kill epithelial and possibly epidermal cells, which cover the surfaces of the genitals; and (3) in at least some users, they apparently increase the risk of infection by HIV, apparently due to the risk of lesions that can damage and breach the epidermal or epithelial layers that protect genital surfaces.

Any or all of these same or similar limitations also apply to various other (non-surfactant) types of toxins. For example, skin irritation caused by microbicides in topical formulations is an important problem, since one of the main distinguishing traits of such microbicides is that they are, by their very nature, toxic (i.e., they were selected for such use because they kill certain types of pathogens). Although some microbicides applied topically to skin surfaces are highly selective and specific in their mode of action (such as certain highly specific drugs used to treat yeast infections, in women), most microbicides in topical formulations that are selected for use on genital surfaces are much less specific, and are designed to kill a broader range of microbes. There exist many similarities between microbial cells and mammalian cells (e.g., both classes of cells are enveloped by membranes formed of lipid bilayers; both classes use the same general processes to form proteins by using DNA, RNA, and ribosomes; both classes contain various similar cellular compartments, and use similar chemical cycles to convert sugar into energy; and there are other similarities, as well). Because of these similarities, compounds that are toxic to

microbes often also inflict some level of toxicity, irritation, or other damage to human cells, including epidermal and epithelial cells.

To help explain this fact, an analogy is appropriate: nearly any type of pesticide (such as an insecticide or fungicide) is dangerous and potentially toxic to certain vertebrates (including humans and various pets, birds, and other vertebrates), even though the quantities that cause genuine toxicity in such vertebrates are usually much higher than quantities that are lethal to insects or fungus. In the same manner, topically-applied drugs that are designed to kill microbes also tend to be irritants, when spread repeatedly on skin, especially on highly sensitive and tender areas of skin, such as genital mucous membranes. Along those lines, it should be recognized that most microbes have evolved in ways that render them quite capable of opportunistic survival, even in highly hostile environments. By contrast, most mammalian cells can survive only in very carefully controlled environments.

For all of these reasons, irritation to genital surfaces is a frequent problem and chronic concern whenever topical microbicides are applied to genital surfaces, for purposes such as treating sexually transmitted diseases, or reducing the risk of infection by such diseases.

In addition, although skin irritation has not received sufficient attention by researchers studying immunology and allergic reactions, physical irritation to the skin can be an important contributing factor which increases both the risk and the severity of allergic reactions to latex articles (including latex condoms) that contact the skin. Accordingly, as discussed in detail below, zinc-containing lubricant formulations that reduce the level of physical irritation to the genitals, during intercourse, also reduce the risk of an allergic reaction to latex condoms. Indeed, as discussed below, certain interactions between zinc and histamine (a natural hormone that severely aggravates inflammatory and allergic reactions) cause certain types of zinc compounds, if added to genital lubricants, to reduce the risk of allergic reactions to latex condoms.

Various zinc compounds are effective as skin protective agents. Zinc oxide (which is not a salt, but which releases zinc slowly when in contact with biological fluids) is the principal agent in calamine lotion, and is also present in many types of ointments and creams used to treat diaper rash in infants, or to treat bedsores and other types of skin ulcers among the elderly and infirm. The skin-protective properties of various zinc compounds (including zinc oxide as well as various zinc salts) are discussed in numerous articles, including Savlov et al 1962, Pories et al 1967, Husain 1969, Henzel et al 1970,

Hallbook et al 1972, Stromberg et al 1984, Apelqvist et al 1990, and Agren 1993; review articles which focus upon zinc's effects on the skin include Agren 1990 and Lansdown 1995. Other articles, which discuss how zinc helps protect cells on a cellular and molecular level, include Chvapil 1973, Chvapil 1976, Mahadevan et al 1990, Bray and Bettger 1990, Pasternak et al 1992, Kaszuba and Hunt 1990, Pasternak 1990, Meftah et al 1991, Zalewski 1991, and Hennig et al 1992.

Chvapil et al 1978a and Chvapil et al 1978b reported the testing of zinc sulfate and copper sulfate (separately) as possible additives in collagen sponges for insertion in the vagina. However, these tests did not discuss or suggest the possibility that zinc might be able to reduce irritation caused by spermicides or microbicides, or reduce allergic reactions to latex condoms. Williams 1980 also reported the testing of potential contraceptives employing zinc salts. However, like the articles by Chvapil et al, the article by Williams did not discuss or suggest the possibility that zinc might be able to reduce irritation caused by spermicides or microbicides, or reduce allergic reactions to latex condoms.

Zinc has never previously been proposed for use to reduce the irritation caused by spermicidal and/or microbicidal toxins in condom lubricants or other topical genital formulations used during sexual intercourse, nor has zinc previously been proposed for use to reduce allergic reactions to latex condoms. However, certain types of zinc compounds have recently been discovered to be well-suited and effective for such use.

Accordingly, one object of the current invention is to provide improved formulations for condom lubricants and other topical genital formulations (as defined below) that contain spermicidal or microbicidal toxins/irritants. These improved formulations also contain zinc, preferably in the form of a water-soluble zinc salt, as a skin-protective additive in such lubricants, to reduce the risk of lesions and other breaches in skin (which, as used herein, includes both epidermal skin, and mucous membranes).

Another object of this invention is to provide improved condom lubricants and other topical genital formulations that contain spermicidal or microbicidal toxins/irritants, by disclosing that certain types of zinc compounds, when used as additives in such formulations, can reduce the irritation caused by such toxic agents.

Another object of this invention is to provide an improved formulation for condom lubricants and other topical genital formulations that contain spermicidal or microbicidal toxins/irritants, by disclosing that certain types of zinc compounds, if used as additives in such formulations, can promote better skin tone, and better long-term genital health and

hygiene, among users whose genitals are repeatedly exposed to irritation and potential surface damage by such toxic agents.

Another object of this invention is to disclose that certain types of zinc compounds can reduce the irritation caused by surfactant spermicides and other microbicides in topical genital formulations, including contraceptive gels used with diaphragms or inserted deep into the vagina by means of insertion applicators.

Another object of this invention is to disclose that certain types of zinc compounds can reduce both the risk and the severity of an allergic reaction to the latex proteins in latex condoms.

These and other objects of the invention will become more apparent through the following summary and description.

SUMMARY OF THE INVENTION

This invention discloses that certain types of zinc compounds, if added to formulations (such as condom lubricants and lubricant gels) that are applied topically to one or more genital surfaces during sexual intercourse, can reduce the irritation caused by spermicidal and/or microbicidal agents, which act essentially as toxins designed to kill various types of cells and microbes. Preferred zinc compounds include zinc lactate, zinc gluconate, zinc acetate, and other water-soluble organic zinc salts. In addition to reducing irritation caused by surfactants (such as nonoxynol or octoxynol) and other microbicides in topical genital formulations, zinc-containing additives can help stabilize and protect cellular membranes, thereby helping protect genital surfaces against damage caused by repeated exposure to agents that attack the lipid membranes that surround mammalian cells. Zinc-containing additives can also help accelerate the healing and closure of lesions or other skin breaches caused by spermicidal or microbicidal toxins, or by abrasion, rashes, sexually transmitted diseases, or other causes. Because of these effects, topical genital formulations containing spermicides or microbicides, and also containing a suitable zinc compound, can promote better skin tone and better genital health and hygiene, compared to similar formulations containing a spermicide and/or microbicide without zinc. In addition, zinc-containing additives can also reduce the risk and severity of allergic reactions to latex proteins in condoms.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

This invention involves skin-protective zinc additives for topical genital formulations which contain a spermicide and/or a microbicide. As discussed in the Background section, above, spermicides and microbicides (referred to collectively as toxins, as mentioned above) can cause physical irritation, annoyance, distraction, and a diminution of pleasure during intercourse, in a substantial portion of the population.

As used herein, "topical genital formulations" (as well as the equivalent terms "topical formulations", "genital lubricants", and "lubricants") refers to topically-applied formulations that are used in connection with sexual intercourse (which term is coextensive and synonymous herein with "intercourse", and includes vaginal, oral, and anal intercourse). Such formulations include but are not limited to: (i) condom lubricants, which (as defined and used herein) are lubricant formulations that are pre-packaged inside packages that also contain one or more condoms; (ii) so-called "stand-alone" gels and other lubricants, which can be used with condoms if desired but which are packaged without condoms, in tubes, bottles, single-dose sealed packets, and other suitable types of packaging; and (iii) formulations containing a spermicide and/or microbicide, which are inserted deep inside the vagina (such as contraceptive gels, foams, or suppositories), either with or without an accompanying diaphragm, in a manner which causes the spermicide or microbicide to block access by sperm or microbes into the uterus. A distinguishing trait of all of these topical formulations is that they are designed to directly contact and form a coating layer on a skin surface (which, as used herein, includes epithelial as well as epidermal membranes). For example, a stand-alone gel can be spread across the surface of the penis immediately before intercourse; similarly, a condom lubricant will be spread across the surface of the penis when the condom is placed on the penis.

Topical genital formulations also include agents that contact only one genital surface during intercourse, including (i) gels, liquids, and other formulations that are spread across the external surface of a condom, after the condom has been placed on the penis, so that the formulation contacts the vaginal membranes but never actually contacts the surface of the penis; and, (ii) gels, foams, creams, and other formulations that are placed inside a diaphragm cup before the diaphragm is placed inside the vagina. Such formulations can be emplaced or applied prior to intercourse (such as by use of a collagen sponge or a meltable waxy suppository, which is designed to be inserted into the vagina up to several hours before intercourse), so that the spermicidal agent will be properly in place during

intercourse. Gels, liquids, and other formulations that are used topically during oral or anal intercourse, or during genital foreplay, are also "topical genital formulations" as defined herein.

This invention also applies to spermicide-containing and microbicide-containing topical formulations that can be inserted or otherwise applied after intercourse, such as to minimize the possibility of pregnancy when proper precautions were not used. In general, any such topical formulation should be in place by the time intercourse begins, for maximum efficacy; however, it is recognized that in some situations, the use of a spermicide or other microbicide after intercourse has finished may be better than having no protection at all. Accordingly, this invention covers spermicide-containing and/or microbicide-containing topical genital formulations, regardless of when they are (or are intended to be) used in connection with intercourse.

As used herein, the terms "surfactant", "surfactant spermicide" and "spermicidal surfactant" (which are equivalent and coextensive, as used herein) refer to any agent that (1) is incorporated into a topical genital formulation, as defined above; and (2) acts as a spermicide by disrupting the membranes that surround the heads of sperm cells. Such agents include ionic surfactants (such as benzalkonium chloride), non-ionic surfactants (such as nonoxynol and octoxynol), and other surface active agents which are incorporated into topical genital formulations and which act as spermicides by disrupting the membranes that surround sperm cells.

Spermicidal surfactants can be divided into arbitrary subclasses, if desired, such as by molecular weight or by number of carbon atoms. However, such arbitrary subclasses are not relevant herein, and the defining attribute of a surfactant, for all purposes herein, is that it acts as a spermicide by disrupting the membranes that surround the heads of sperm cells.

Terms such as "reducing irritation", "a reduction in irritation", and "a reduced tendency to cause irritation" include any reduction in the frequency, prevalence, or severity of irritation, for at least some users. For example, if 10% of users notice irritation when a certain formulation containing a spermicide or microbicide is used, and only 5% of users notice irritation after a certain zinc salt is added to that same formulation, that result is regarded as a reduction in irritation. Similarly, a reduction of irritation is deemed to occur if a zinc additive reduces short-term, intermediate-term, or long-term irritation (as discussed in more detail just below) by a spermicide or microbicide.

Three different types or levels of irritation can be caused by spermicides or

microbicides in topical genital formulations, depending on the time scale that is being considered. At the shortest end of the time scale, "short-term" irritation refers to irritation that occurs during intercourse, or within a short time span thereafter (such as half an hour). This type of short-term irritation usually involves a burning or unpleasant tingling sensation, or an otherwise distracting and annoying sensation or awareness of an unnatural and undesired chemical which coats one or more genital or mucosal surfaces. In some men, this type of irritation is not evenly distributed across the entire penis, but is present mainly in the exposed mucous membrane surfaces at or near the tip of the urethra.

In the middle of the time scale, "intermediate-term" irritation refers to a sense of irritation, genital soreness, or a lack of desire for intercourse, that accumulates over a span of several days, if a topical formulation containing a spermicide or microbicide is used each day or nearly every day.

"Long-term" irritation, as used herein, refers to lesions and other physiological damage to skin when a topical genital formulation containing a spermicide or microbicide is used repeatedly over a span of weeks or months.

Accordingly, "irritation" as used herein means irritation of the skin (as defined above, this includes mucous membranes), and refers to any combination of short-term, intermediate-term, and/or long-term irritation experienced by a user of a topical genital formulation containing a spermicidal or microbicidal toxin.

INDUSTRIAL UTILITY

The industrial utility of this invention involves the manufacturing or other commercial preparation of topical genital formulations having reduced irritation levels and reduced danger of latex allergy reactions, for sale to the public. In general, the invention discloses a method of incorporating, into a condom lubricant or other topical genital formulation containing a spermicidal or microbicidal toxin, an amount of a pharmaceutically acceptable zinc compound which is effective in reducing irritation caused by such toxin.

In another aspect, this invention discloses a composition of matter, comprising a topical genital formulation containing a spermicidal or microbicidal toxin, and also containing a pharmaceutically acceptable zinc compound in an amount which is effective in reducing irritation caused by the toxin, and reducing allergic reactions to latex condoms.

This invention also discloses an article of manufacture comprising a zinc-containing and toxin-containing topical genital formulation packaged in a tube, a single-dose sealed

watertight packet, or other suitable container, or pre-packaged with a condom inside a sealed watertight packet.

In another aspect, this invention discloses a method of reducing irritation caused by a spermicidal or microbicidal toxin in a topical genital formulation, by means of topically applying a topical genital formulation containing an amount of a pharmaceutically acceptable zinc compound which is effective in reducing irritation caused by the toxin.

In other aspects, this invention discloses compositions, articles of manufacture, and methods, relating to the manufacture and sale of condom lubricants and lubricated condoms that can reduce the frequency and severity of allergic reactions to latex condoms, regardless of whether a condom lubricant contains a spermicidal or microbicidal toxin.

RECENT TEST RESULTS

Recently, during a set of genital irritation tests, it was discovered that certain zinc salts (zinc lactate and zinc gluconate) reduce the physical irritation caused by nonoxynol, during intercourse.

This was a completely unexpected property; although the advantages of zinc as an anti-viral agent had previously been recognized and disclosed, there was no reason to believe or suspect that zinc lactate or zinc gluconate might actually be able to make nonoxynol (a surfactant that is widely used as a spermicide in condom lubricants and other topical genital formulations, as discussed above) less irritating and annoying, when the two agents (i.e., nonoxynol, on the one hand, and zinc lactate or zinc gluconate, on the other hand) were combined with each other in a lubricant formulation. The test procedures and formulations that were used to evaluate and confirm this effect (i.e., substantially lower levels of irritation) are described below, in the Examples.

Because of their chemical structure, surfactants such as nonoxynol act in an aggressive manner. Instead of targeting only one class of cells, surfactants attack and disrupt lipid bilayer membranes, which surround and enclose many types of cells. Such membranes enclose epithelial cells (which cover relatively sensitive and vulnerable mucous membranes), and epidermal cells (which cover conventional skin surfaces). Epithelial and epidermal cells are therefore directly vulnerable to damage and irritation by surfactants, not just because of peripheral side effects, but because of the fundamental membrane-attacking activity of surfactants.

Accordingly, in terms of causing irritation, surfactants rank among the most difficult

and problematic of all spermicides and microbicides used in topical genital formulations, and any agent that can reduce the irritation caused by surfactants has shown that it can, in effect, jump over a high and difficult hurdle.

As disclosed herein, zinc compounds have been shown to be effective in reducing irritation caused by the types of surfactants which pose a very difficult challenge, since they directly attack epithelial membrane and epidermal skin cells. Therefore, these zinc compounds can also help reduce irritation caused by other spermicides and microbicides that generate fewer and/or lesser problems of irritation. By way of analogy, a runner who can jump over a high hurdle can also jump over smaller hurdles, with room to spare.

As discussed in more detail below, the term "zinc compound" is used herein to include zinc salts, zinc complexes, and other chemical substances containing zinc which are suitable and effective for use as disclosed herein.

The results of the tests described in the Examples indicate that suitable zinc compounds (such as zinc lactate or gluconate) can reduce genital irritation caused by a toxin (in this instance, the surfactant spermicide, nonoxynol) during intercourse. Briefly, in one test (all tests were carried out by a monogamous married couple who are free of any known sexually transmitted diseases) using a contraceptive gel containing 4% nonoxynol, without zinc, the gel caused a substantial and seriously unpleasant tingling sensation in the male, who is relatively sensitive to nonoxynol irritation. This annoyance persisted throughout intercourse, and was a continuing distraction. The female, who does not suffer from a high level of sensitivity to nonoxynol irritation, regarded the 4% nonoxynol gel as noticeable and "borderline unpleasant" if she paused to think about it; however, it was not especially irritating or distracting to her.

In a subsequent test, the same gel with 4% nonoxynol was supplemented by zinc lactate. The female did not report any significant change when zinc was added. However, the male (who is more susceptible to nonoxynol irritation) reported a major improvement; the 4% nonoxynol gel containing added zinc lactate was substantially less irritating, less noticeable, and less distracting; in all respects, it was substantially preferable to the same 4% gel without zinc.

A second series of tests was also carried out using gel containing 3.1% nonoxynol. This gel, which was formed by mixing equal portions of a 2.2% gel and a 4% gel, was somewhat less irritating to the male than the 4% gel, and this mixed gel allowed tests to be carried out on several successive nights, with and without zinc lactate. When the 3.1% gel

without any zinc was used as a lubricant during intercourse on three successive nights, the male noticed a feeling of lingering irritation in the genitals by the second and third days, and felt a diminution of sexual interest each day, leading to a complete absence of any desire for intercourse by the fourth day. By contrast, when the same tests were carried out on three successive nights using the same 3.1% gel supplemented with zinc lactate, there was no feeling of lingering physical irritation after the third night, and no noticeable loss of sexual interest or appetite.

Both results indicate that zinc lactate can significantly reduce both short-term and intermediate-term irritation, caused by an important type of toxin/irritant (nonoxynol) that is widely used as a spermicide and which is also a microbicide.

Similar tests using the same gels supplemented by zinc gluconate were also carried out. The results of these tests were identical to the results obtained with gels containing zinc lactate, indicating that zinc gluconate also substantially reduces irritation caused by a toxin/irritant which is a surfactant spermicide and a microbicide, as well.

As noted above, this reduction of irritation was completely unexpected.

REDUCING THE RISK AND SEVERITY OF LATEX ALLERGY REACTIONS

It also has been discovered that various zinc compounds which are effective in reducing irritation caused by spermicidal or microbicidal toxins are also effective in reducing both the risk and the severity of allergic reactions to latex condoms.

Allergic reactions to latex are caused by certain proteins found in latex, which is derived from natural sources (primarily from sap obtained from certain types of trees). The chemistry and biochemical reactions involved in latex allergies are discussed in detail in numerous published articles, such as Losoda et al 1992, Oei et al 1992, Gold et al 1993, Pecquet et al 1993, and Harmon et al 1995. Latex allergies are an important public health problem, since (i) they directly harm a significant number of people, and have even caused death or permanent and severe brain damage in numerous cases; and (ii) they render people who have suffered an acute episode completely unable to use latex condoms, thereby increasing the risks of sexually transmitted diseases and unwanted pregnancies.

Acute allergic reactions involving latex are most commonly provoked by contact with latex gloves, rather than latex condoms. Nevertheless, the gradual buildup of a sub-acute (latent) problem that leads to gradual hyper-sensitization of the immune system, which in turn prepares the immune system for an acute and potentially deadly allergic reaction,

can be accelerated and worsened by repeated exposure to latex condoms, prior to an acute crisis. Therefore, even though acute allergic reactions to latex condoms are rare, frequent and repeated exposure to latex condoms contributes to the sharply increasing number of acute latex allergy reactions that are being reported worldwide.

A number of efforts have been made to prevent or minimize allergic reactions to latex, usually by means such as (1) chemical treatment to reduce or modify allergenic proteins in the latex, as described in US patents 5,563,241 (Beezhold 1996) and 5,549,924 (Lester et al 1996); and (2) creating gloves or condoms having multiple layers (e.g., US patents 5,549,924, above, and 5,636,382, by Chopko et al 1997). However, all such methods suffer from various drawbacks. For example, chemically processing of large quantities of raw latex to remove latex proteins is expensive, while multi-layered condoms cause decreased sensitivity and pleasure, leading to greater reluctance on the part of users to wear them. Prior to this invention, there has been no adequate solution to the problem of allergic reactions to latex condoms, or latex gloves.

Accordingly, this invention discloses a new method for reducing the frequency and severity of allergic reactions to latex condoms. As used herein, "frequency" of allergic reactions refers to (i) the number, frequency, or rate of occurrences of latex allergy reactions in a population of latex condom users; (ii) the likelihood of a latex allergy reaction in a latex condom user who has not previously experienced such an episode; and (iii) the frequency of allergic episodes in a latex condom user who becomes hypersensitized. Accordingly, terms such as "reduction of frequency", "reduced frequency", and "reduce/reducing the frequency" include a reduction in one or more of these three parameters. Similarly, "severity" refers to the magnitude, duration and effects of an allergic reaction, as measured by relevant factors, including, for example, (i) the peak or average intensity of an allergic response, as indicated by parameters such as the extent of redness, reported pain levels, analyses of white blood cell concentrations, or changes in vital signs such as respiration, heartbeat, or blood pressure; (ii) the duration of such effects; (iii) the duration and severity of lingering after-effects, once the primary reaction has subsided; (iv) the degree or extent of the person's hypersensitivity to subsequent contact with latex allergens or antigens; and (v) the tendency of such allergic reactions to trigger other medical problems, such as outbreaks of herpes, lupus, or other chronic conditions. Thus, as used herein, terms such as "reduction of severity", "reduced severity" and "reduce/reducing the severity" include any reduction, as measured by one or more of those

relevant factors, in the severity of an allergic reaction. A reduction in either the frequency of allergic reactions to latex condoms, or the severity of such allergic reactions when they occur, would be highly useful and beneficial. Accordingly, phrases such as "reduce/reducing allergic reactions to latex condoms" refer to a reduction in the frequency and/or the severity of such reactions.

A number of cellular and physiological factors and processes help explain how zinc compounds, in condom lubricants, can reduce the frequency and severity of allergic reactions to latex condoms.

One of these factors involves the ability of zinc, when applied topically to the surface of skin, to promote and accelerate the healing of lesions, abrasions, wounds, and other skin deficits. These protective effects of topical zinc are long- known and well-established; as mentioned above, zinc is the active ingredient in calamine lotion, and in virtually all ointments spread on baby bottoms and genitals to treat diaper rash.

These soothing, healing, protective activities of topical zinc (in suitable formulations) can be quite valuable in reducing and preventing allergic reactions to latex condoms, because of an important aspect of the immune system. In general, two things have to occur to provoke an allergic response, in a healthy person. First, some sort of foreign protein or other antigen must be present. And second, something must happen which causes the body's defensive mechanisms to mount a full-scale defense which tries to destroy the invading molecules.

By way of analogy, a police officer will not arrest someone for carrying an illegal weapon or drugs, unless and until something happens which brings the illegal actions or condition to the attention of the police. Police do not, and cannot, continuously monitor the status of every person in an entire city or continent. Similarly, an immune system cannot continuously monitor the status of every cell or molecule in the body. Something needs to happen which calls attention to a problem, before any particular type of molecule triggers the type of cellular chain reaction which can lead to a full-scale allergic or immune response. This is why, for example, when an antigen is injected into a lab animal for the purpose of generating an immune response, the antigen is mixed with a solution such as "Freund's adjuvant", which contains compounds that deliberately irritate the animal's tissue at the injection site. The irritant compound in the adjuvant creates a localized inflammation. When the animal's immune system begins sending large numbers of white blood cells to the inflammation site, to help combat the problem, some of those white blood cells encounter

the foreign antigen, and begin making antibodies that help destroy that antigen.

This process helps explain how and why suitable zinc compounds reduce the likelihood of an allergic reaction to latex, if they act as skin-soothing, skin-protective agents. By minimizing irritation and/or inflammation of the skin, they reduce the quantities of white blood cells that are sent to the site of irritation. This reduces the amount of contact between latex proteins (which are foreign) and white blood cells that are searching for foreign proteins.

Another important factor which helps explain how zinc reduces the frequency and severity of allergic reactions to latex involves a biochemical molecule called histamine, which is well-known to people who suffer from runny noses, watery eyes, and the other symptoms of hay fever. Histamine is one of the most important intercellular messenger molecules, when it comes to both (1) tissue injuries, such as cuts and bacterial infections, and (2) allergic reactions. It is released, in large quantities, by certain types of white blood cells called mast cells. It also is released by ruptured cells, in injured tissue.

After being released, histamine triggers a complex series of cellular reactions, some of which increase local blood flow and increase the permeability of capillaries in the region. These two effects allow blood serum and proteins to leak out of the capillaries, and seep into the surrounding tissues. These blood fluids clot, and effectively try to "wall off" the affected area. This "walling off" process can be extremely useful, if the body is trying to delay the spread of deadly bacteria or toxins which have entered a cut or other wound. However, this same process can be extremely annoying, when it happens during an allergic reaction such as hay fever.

Accordingly, anti-histamines are used by many millions of people, to help treat hay fever and other allergic reactions, and to treat colds, flu, and other viral infections that cause similar symptoms. Some anti-histamines work by reducing the amount of histamine released by various types of cells; others work by binding to already-released histamine in the blood, thereby preventing it from reacting with target cells to cause its inflammatory effects.

Compounds that release zinc ions have three distinct effects on histamine, and these effects all reduce the concentration of free histamine in blood or other body fluids.

First, if a suitable zinc compound is added to a lubricant used with latex condoms, the zinc reduces the amount of histamine released by damaged cells on or near the surfaces of the skin or mucous membranes. These surface and near-surface skin cells can be

ruptured (thereby causing them to release histamine) by various mechanisms, including (1) abrasion; (2) chemical assault, such as by detergent-type spermicidal surfactants such as nonoxynol, by the acidic fluids in the vagina, and by metabolic byproducts from yeast and bacteria in the vagina and elsewhere on the skin; and, (3) lesions caused by sexually-transmitted diseases, such as herpes or syphilis, and by other infections, such as yeast or fungal infections in women. By helping accelerate the closure and healing of such abrasions, lesions, and other skin deficits, a zinc compound added to a condom lubricant can reduce the amount of histamine released by the damaged skin cells.

Secondly, zinc reduces the quantity of histamine released by certain types of white blood cells, called mast cells (see Kazimierczak et al 1974). Mast cells contain large quantities of histamine, and play a major role in histamine release in response to injury or inflammation.

And third, zinc ions form molecular complexes with free histamine molecules in bodily fluids (Mickel et al 1955; Holmes et al 1960). This effectively entangles the histamine, changes its chemical binding characteristics, and reduces its ability to provoke its "walling off" activities.

All of these actions contribute to reductions in (i) the amount of histamine that is released by cells; (ii) the amount of swelling and inflammation that histamine can provoke; and (iii) the ability of histamine to provoke or aggravate an increased immune or allergic response, in a localized area of tissue.

For all of the foregoing reasons, suitable zinc compounds, when added to lubricants that are used with latex condoms, reduce the frequency and severity of allergic reactions to the latex in such condoms.

PREFERRED ZINC COMPOUNDS

Preferred zinc compounds for use as disclosed herein include organic zinc salts with relatively low molecular weights (such as less than about 800 to 1000 daltons; for comparative purposes, the molecular weight of zinc gluconate is about 456 daltons). These salts include zinc acetate, zinc butyrate, zinc formate, zinc gallate, zinc gluconate, zinc glycerate, zinc glycolate, zinc lactate, zinc propionate, zinc pyruvate, and various other known salts of carboxylic acids. Salts made from di-carboxylic acids (i.e., molecules with two carboxy groups) can also be used; examples include zinc maleate, zinc malonate, and zinc succinate.

The traits that render various salts preferred for use as disclosed herein include: (1) a substantial level of solubility in water; (2) a significant rate of ionic dissociation in aqueous solution, so that free zinc ions (Zn^{++}) will be released into solution; (3) physiological acceptability at the relevant concentrations, when used in a topical genital formulation that will be used repeatedly, during each act of intercourse, over a period of months or possibly years; and (4) absence of unacceptable color, odor, or other undesired properties when added at the relevant concentration to a topical genital formulation as disclosed herein. In addition, a zinc salt for use as disclosed herein preferably should be clear, rather than strongly colored or opaque, to avoid or minimize staining of clothes or bedsheets.

One salt that is especially preferred for use as disclosed herein is zinc lactate, since it releases lactate ions. Lactate ions are naturally present at high concentrations in any healthy vagina, since the vagina secretes relatively high quantities of lactic acid, to help suppress pathogenic yeast, fungal, and other microbial infections. Therefore, the epithelial and epidermal membranes of the genitals, and the natural and healthy microbial flora that normally inhabit a vagina and help suppress other pathogenic microbes, are well-adapted to coping with large quantities of lactate ions.

Zinc gluconate (ZnGlu), which is widely used in zinc mineral supplements and other formulations that are ingested, was stated to be a non-preferred embodiment in the anti-viral lubricant patents issued to Kelly, cited above, because of the relatively low solubility of zinc gluconate in water. However, that conclusion was based on tests carried out in the late 1980's or early 1990's, which used a preparation of granular ZnGlu purchased from Ruger Chemical Company (Irvington, New Jersey). Even when ground up for prolonged periods using a mortar and pestle containing several drops of water, the supply of zinc gluconate purchased in the late 1980's left a residual grit, which rendered it non-preferred for a topical genital formulation, since any grit in a genital lubricant poses a severe risk of abrasion and damage to the genital surfaces.

However, a new and different supply of zinc gluconate was purchased in mid-1997 from Amend Chemical Company (Irvington, New Jersey). While the earlier supply (purchased in the late 1980's) had been a gritty, granular, coarse-grained preparation, the 1997 supply was a much finer powder. This powdered preparation was much more soluble in water; when stirred for several seconds in a few drops of tap water or distilled water, the powdered ZnGlu dissolved completely and left no detectable residue of gritty particles,

either before or after the slurry was mixed with a lubricating gel.

The Applicants subsequently learned that several chemical suppliers (including Amend Chemical Company, and Generichem, located in Totowa, New Jersey) sell zinc gluconate in both granular (gritty) form, and in powdered form. The granular form is preferred for many manufacturing processes, since it does not generate as much airborne dust as the powdered form; it can be used, if desired, in a lubricant as disclosed herein, if a solubilizing agent is also added to the mixture. In general, the powdered form is preferred for use as described herein, since it is more readily and easily soluble in water, and requires less effort and expense to completely solubilize it in a lubricant formulation, without any requirement for an additional solubilizing agent.

It also should be noted that zinc pyruvate releases pyruvate ions, which are a substrate that cells use to generate energy during the process of glycolysis. Pyruvate is the intermediate that feeds the so-called "Krebs cycle", in which the metabolites formed from glucose are broken down to carbon dioxide and water, to release large quantities of energy. By providing an active agent that can boost cellular metabolism, zinc pyruvate in a topical genital lubricant may be useful in treating various urinary, gynecological, dermatological, or sexual disorders, such as impotence and post-menopausal discomfort.

If an inorganic salt such as zinc chloride or zinc sulfate is used, steps preferably should be taken to reduce or minimize the irritation such a salt can cause in the absence of such steps. Factors that should be kept in mind include the following.

First, zinc chloride and zinc sulfate ionize at very high rates (at levels approaching 100%, releasing essentially all of their zinc in the form of free divalent ions) when dissolved in an aqueous solution. By contrast, even the most highly ionizing organic salts (such as zinc acetate) tend to ionize at rates of about 30% or less (as indicated by pK values of about 1, or higher). Accordingly, smaller quantities of zinc chloride or zinc sulfate (or various other inorganic salts) are required to provide a given concentration of zinc ions, compared to the quantities of organic salts required to provide the same level of ions. This simple factor (i.e., a reduction in the quantity of the salt) can reduce or avoid irritation caused by a highly ionizing inorganic salt such as zinc chloride or sulfate.

Second, highly-ionizing zinc salts, when dissolved in an aqueous solution, will make the solution acidic. When positively charged zinc ions are dumped into solution by a highly-ionizing salt, the Zn^{++} ions bind with negatively-charged hydroxyl (OH^-) ions, which are released when water molecules spontaneously dissociate into H^+ and OH^- ions. This

binding, between Zn^{++} ions and OH^- ions, reduces the number of free OH^- ions. This in turn increases the number of "stranded" hydrogen protons (H^+) in the solution, since those ions no longer have a balanced number of OH^- ions with which they can interact. This increase in H^+ ions is, quite simply, an increase in acidity, since acidity in an aqueous solution is a direct measurement of H^+ ion concentration. It is not the Zn^{++} ions in solution which irritate the skin; instead, it is the increase in acidity caused by binding of the zinc ions to OH^- ions. Accordingly, highly ionizing salts such as zinc chloride or sulfate, which release more Zn^{++} ions cause greater acidity, compared to organic zinc salts.

As a demonstration, when 5% (weight per volume) solutions were prepared from zinc acetate and zinc lactate in distilled deionized water, the pH of each solution was about 6.2. By comparison, when a 5% solution of zinc sulfate was prepared, its pH was about 5.6. Since the pH scale is logarithmic, and a drop of 1 pH unit indicates 10-fold greater acidity, a pH drop of 0.6 (from 6.2 to 5.6) indicated about 4 times as much acidity in the zinc sulfate solution as in the zinc acetate or lactate solutions.

In a genital lubricant, this increased acidity can be eliminated or minimized by adding a neutralizing or buffering agent to the lubricant formulation. A neutralizing agent is an alkaline compound (such as NaOH, sodium hydroxide) that releases OH^- ions (along with a stable and non-irritating cation, such as Na^+) in sufficient quantities to neutralize or at least reduce the increase in acidity caused by an acidifying agent such as zinc chloride or sulfate.

A buffering compound (such as $NaHCO_3$, sodium bicarbonate) partially dissociates at a neutral pH (pH 7), in a manner that allows its equilibrium dissociation levels to be pushed in either direction, by either an acid or alkali. If an acid is added to a solution containing a buffer, the buffer will be pushed in a direction that minimizes the effects of the acid, to help keep the pH of the solution relatively stable and close to neutral. Conversely, if an alkali is added to a solution containing a buffer, the buffer will shift in the opposite direction, thereby minimizing the effects of the alkaline compound and helping keep the pH of the solution relatively close to neutral.

Various neutralizing and buffering agents known to those skilled in the art are physiologically acceptable and otherwise suitable for a topical genital lubricant formulation. As one example, K-Y Lubricating Jelly contains a strong alkali, sodium hydroxide (NaOH), as a neutralizing agent to reduce the acidity of other components of K-Y Jelly. By itself, sodium hydroxide is lye, which is extremely irritating to the skin. However, if added to an

acidic mixture, a proper quantity of sodium hydroxide simply neutralizes the acid and prevents the acid from causing irritation.

Accordingly, highly-ionizing salts (including inorganic salts such as zinc chloride or sulfate, as well as organic salts such as zinc acetate or propionate) can be used in genital lubricants. If the concentration of a highly-ionizing zinc salt in a lubricant causes undesired acidity, the acidity can be reduced by any or all of several techniques, including: (i) limiting the quantity of the highly-ionizing salt; (ii) using two or more salts in combination; and (iii) adding a neutralizing or buffering agent.

In addition to the various salts listed above, other zinc compounds (including various zinc "complexes") are also suitable for use as disclosed herein. These include various zinc complexes listed and shown in articles such as Merluzzi et al 1989, which tested a large number of zinc salts and complexes in order to rank their anti-viral activities in cell culture tests. In general, "complexes" is a vague and imprecise term when used in the context of molecules that contain metal atoms; it generally refers to molecular compounds that contain one or more metal atoms, but which do not release the metal ions into solution as readily as other compounds which are deemed to be "salts". Although arbitrary classifications that depend on numerical pK levels are used by some researchers to create arbitrary boundary lines between zinc salts and zinc complexes, there is no natural dividing line between a zinc salt and a zinc complex. Accordingly, any zinc complex which releases free zinc ions (Zn^{++}) in significant quantities, in aqueous solution, is regarded herein as a zinc salt.

If a non-salt zinc compound (such as zinc oxide, as one example) is added to a topical formulation as disclosed herein, along with a solubilizing agent that weakens or otherwise alters the chemical bond(s) between the zinc and the covalently bound atom(s) in the compound, thereby causing release of significant quantities of free zinc ions from the zinc compound in the presence of the solubilizing agent, the net result is functionally equivalent to providing a zinc salt as a single initial ingredient. Accordingly, if a mixture of such reagents (i.e., a non-salt zinc compound, plus a solubilizing agent) is added to a topical genital formulation as disclosed herein, such a combination is regarded as the addition of a zinc salt to the formulation.

ZINC CONCENTRATION RANGES

Rather than trying to determine a single concentration of a zinc salt that would be optimal for everyone, the effectiveness of this invention can be enhanced by providing

lubricants having a range of different zinc concentrations, for different people. By way of analogy, since some people are easily sunburned while others are highly tolerant of direct sunlight, suntan oils and creams are sold with a range of "sun protection factors." Anyone is free to choose his or her preferred formulation, based on skin type, anticipated exposure levels, and other factors. As another example, contraceptive gels ranging from 1% to 4% nonoxynol, and condoms lubricated with fluids ranging from 5% to 15% nonoxynol, are sold over-the-counter. Purchasers are free to choose the concentration they prefer.

In a comparable manner, genital lubricants having a range of concentrations of zinc salts can be made available, and people can choose the concentration they prefer, depending on various factors, including personal preferences and the type of lubricant they are using.

In lubricants that contain nonoxynol or other spermicidal or microbicidal toxin(s), in which a zinc salt is included to reduce the irritation caused by the toxin, the preferred concentration of organic zinc salts is in the range of about 0.5% to about 15% (all percentages discussed herein as expressed as weight per volume, w/v, calculated as grams of zinc salt per milliliter of fluid, multiplied by 100 to convert the ratio to a percentage). The preferred concentration for any specific salt will depending to a large extent on the ionizing rate of that salt. Highly-ionizing salts (which have relatively low pK values, such as zinc acetate or propionate) will be at the lower end of the range, while salts with lower ionization levels (higher pK levels) will be at the higher end. If an inorganic salt with even higher ionizing levels (such as zinc chloride or sulfate) is used, the preferred range to reduce the irritation by a toxin will be lower, such as in the range of about 0.03% to about 5%.

Alternately, if a zinc salt is added to a lubricant in order to reduce the risk of allergic reactions to latex condoms, preferred concentration ranges are higher, such as up to about 30% (or even higher) of a zinc compound that has a relatively low ionizing rate. With respect to this 30% figure, it should be noted that:

(1) It indicates the weight of the salt, rather than the weight of elemental zinc. For example, a compound containing 30% w/v zinc gluconate contains only about 4% elemental zinc.

(2) Preparations used for other surface applications are sold over-the-counter which contain more than 30% elemental zinc.

(3) Relatively small quantities of lubricant are typically used in conjunction with condoms. For example, while spermicidal gels for use without condoms usually contain

about 5% or less nonoxynol, many condom lubricants contain up to 15% nonoxynol. Accordingly, a lubricant intended for use with a condom may have a higher concentration of a zinc salt than a lubricant intended for use without a condom.

(4) The lubricant usually becomes diluted by the female's natural fluids after intercourse begins.

CARRIER SUBSTANCES

The carrier substance used in a particular lubricant is not critical to this invention. As described in numerous publicly-available reference works, and in sources such as publicly-accessible filings that have been submitted to the U.S. Food and Drug Administration by companies seeking approval to sell various compounds to the public, a variety of different carrier substances can be used in topical genital formulations. Each such formulation currently in use has been carefully developed to optimize its performance in a particular mode of use. For example, condom lubricants, stand-alone lubricant gels, and viscous gels for insertion deep into the vagina, all have different packaging and performance requirements and goals. For each such use, those requirements and goals have led to variations in the preferred carrier substances. Accordingly, the scientists and health care specialists at any company which manufactures and sells topical genital formulations can adapt the teachings herein to any specific formulation or use.

PACKAGING FOR STAND-ALONE LUBRICANTS

Packaging for the articles of manufacture disclosed herein is not critical to this invention. By way of illustration, a variety of different packages are used for (i) condoms, which are usually packaged in sealed plastic or foil packages with a single condom in each sealed sterile package; (ii) "stand-alone" lubricants; and (iii) viscous gels intended for insertion deep into the vagina, using an applicator.

A "stand-alone" lubricant should be packaged, shipped, and handled in a package that renders it convenient and useful as a genital lubricant, during intercourse. Types of packaging that are commonly used for stand-alone gels and similar formulations include:

(1) A watertight tube made of deformable metallic foil. Such tubes usually are sealed at one end by means such as crimping, and have an outlet orifice at an opposed second end, which can be covered and sealed by a removable and/or openable device such as a threaded or flip-top cap. Such metallic foil tubes are commonly used to hold toothpaste, ointments,

and gels such as K-Y Lubricating Jelly and contraceptive gels. When squeezed to dispense a quantity of lubricant, a deformable metallic tube does not seek to regain its original shape after the squeezing pressure is released. By avoiding the creation of a vacuum inside the tube which would draw air into the tube, this minimizes oxidative discoloration or degradation of the lubricant in the tube. In addition, another advantage of a metallic container in this particular context is that it can be placed in a cup or glass of warm or hot water, such as on a table or nightstand next to a bed. The metallic walls of the tube quickly convey heat from the warm water into the lubricant; this warms the lubricant to a pleasant temperature before it is applied to the genitals. This procedure encourages consistent rather than sporadic use, and can help make the step of applying the warm lubricant a pleasant form of foreplay, rather than a distracting annoyance of a cold fluid on the genitals. Anything which enhances a sense of warm pleasantness when applying such a lubricant helps promote consistent and reliable use.

(2) A watertight tube with deformable plastic walls, permanently sealed at one end (such as by heat-crimping), and a removable cap covering an outlet orifice at the other end. Such tubes are commonly used to hold toothpaste, ointments, and gels such as K-Y Lubricating Jelly and contraceptive gels. The cap can be a threaded screw-on cap, or a hinged flip-type cap which can be opened without detaching it from the tube, so that it cannot be lost, and can be opened or closed easily with one hand. Between the two ends of the tube, the container has at least one deformable plastic wall, which preferably should be essentially tubular, comparable to a toothpaste tube, with a transitional shoulder or neck region leading to the outlet orifice.

(3) A small, flat, watertight packet which contains a sufficient quantity of lubricant for a single use during intercourse (such as about 5 to 10 milliliters, or about 1 to 2 teaspoons). Such packets can be made of plastic, metallized foil, or other suitable material. This type of small sealed packet allows the lubricant to be conveniently and discretely carried in a purse, pocket, glove compartment of a car, or other location without the bulk or conspicuousness of a full-sized tube.

(4) A small single-dose container made of a breakable plastic, ceramic, or other material, which can be opened by breaking off a component that protrudes outwardly from the container, thereby unsealing an outlet orifice. This type of device is comparable to a miniature version of the plastic bottles with break-off tops that are widely used for non-carbonated children's drinks.

(5) A stiff-walled bottle, normally but not necessarily in an upright configuration, with a wall (typically cylindrical or with an elliptical or similar cross-sectional shape) made of plastic, glass, or other suitable material. When such containers have deformable plastic walls, they are simply another form of watertight tube, which can be squeezed when the cap is open to dispense the fluid contained therein. Alternately, such bottles are often equipped with a dispenser-type device (usually mounted on top, as part of a cap assembly) that allows a quantity of the lubricant to be conveniently dispensed when manually operated, such as by depressing a plunger mechanism. Such plunger-type dispensers are widely used for dispensing creams, ointments, fluidized soaps, or other fluids from such bottles. This allows a desired quantity of the fluid to be placed on the palm or fingers of one hand while the other hand remains dry and clean; alternately, it would allow a genital lubricant to be placed directly onto the surface of the penis, without getting any of the lubricant onto either hand.

(6) A vaginal insertion device, which is designed to insert and emplace a gel, foam, or similar fluid deep enough inside a vagina so that the fluid coats and blocks the entrance to the uterus. Such devices, which are widely used with contraceptive gels and foams, typically comprise a cylindrical barrel which is properly sized for comfortable insertion into a vagina. During use, the barrel encloses a slidable plunger or piston component which is manually forced into the barrel from one end, thereby forcing the fluid out of the barrel through an orifice at the other end of the barrel. These insertion devices are commonly sold in two different forms: (1) a disposable single-use form, with a gel-type fluid already loaded inside the chamber, and with the entire article inside a sealed sterile package, for use prior to a single act of intercourse; or (2) a reusable device which is designed to be filled and used repeatedly, prior to each act of intercourse, from a container which holds a sufficient quantity of gel or foam for multiple applications. Either type of device is well-suited for use with zinc-containing lubricants as described herein.

EXAMPLES

EXAMPLE 1: REDUCTION OF SHORT-TERM SURFACTANT IRRITATION, BY ZINC LACTATE

The zinc lactate salt used in these tests contains a racemic mixture of the D and L isomers of lactate (sold by Sigma Chemical Company, St. Louis, catalog number L-1625)

having the molecular formula $Zn(CH_3CHOHCOO)2$ and also containing 1.5 moles of hydration water per mole of zinc.

To determine whether this zinc compound could reduce the irritation caused by nonoxynol in a genital lubricant gel, approximately 0.2 grams of the zinc lactate compound was dissolved in half a drop of water, to form a small quantity of a slurry. This slurry was added to a gel contraceptive containing 4% nonoxynol (0.9 ounce, packaged in single-dose plastic applicators for insertion deep into the vagina; sold under the trademark "CONCEPTROL" by Advanced Care Products, a division of Ortho Pharmaceutical Corporation, which is a subsidiary of Johnson & Johnson, New Brunswick, New Jersey). The mixture was stirred for half a minute using a mortar bowl; it was not necessary to grind up the mixture to remove any particulates, since the zinc lactate was highly soluble in the water and the gel.

A series of escalating tests was used to guard against possible irritation by this mixture. In the first test, the nonoxynol gel containing zinc lactate was tested on the relatively hairless portion of the forearm, in a passive placement test. It did not cause any irritation after being left in place for an hour, so it was tested again on the other forearm, in a test that included active rubbing of the mixture into the skin. This second test did not reveal any irritation, so the mixture was spread on the male genitals, which can be washed off more quickly and easily than female genitals if irritation arises. The first test on the male genitals was a passive placement test. No irritation was observed, so it was followed by a similar test that included active rubbing. No irritation was detected, so it was tested during intercourse.

When a gel containing 4% nonoxynol without any zinc lactate (as a negative control) was used as a lubricant during intercourse by a married couple, it caused a substantial unpleasant tingling sensation in the male, who is sensitive to nonoxynol irritation. This unpleasant sensation lasted throughout intercourse, and was a continuous distraction. By contrast, the female was not as sensitive to nonoxynol irritation, and regarded the 4% nonoxynol gel as being slightly noticeable but not especially irritating, and did not find it a continuing distraction during intercourse.

When the same 4% nonoxynol gel was mixed with 0.2 grams of the zinc lactate salt described above, it reduced (by a substantial degree) the unpleasant tingling sensation felt by the male. The mixture with zinc lactate was still noticeable, but it was not especially irritating or unpleasant. When compared to the 4% gel alone, the addition of zinc lactate

provided a noticeable increase in comfort and pleasure.

When zinc lactate was added to the gel, the female did not notice a substantial reduction in irritation, since she is not highly sensitive to, and had not in the first instance experienced, nonoxynol irritation; nor did she detect any increased irritation.

EXAMPLE 2: REDUCTION OF INTERMEDIATE-TERM SURFACTANT IRRITATION, BY ZINC LACTATE

Because the male volunteer regarded the gel with 4% nonoxynol as genuinely unpleasant and unsuited for consistent and repeated use, he prepared a gel mixture containing 3.1% nonoxynol, by mixing equal quantities of the 4% gel (described above, from a single applicator containing approx. 0.9 ounce), with an equal quantity of a second gel containing only 2.2% nonoxynol (sold in a plastic tube under the trademark "K-Y Plus", by Johnson & Johnson Consumer Products, Skillman, NJ). After using the 3.1% gel mixture on three successive nights, the male noticed a feeling of lingering irritation and unpleasantness in the genitals, with a substantial diminution of sexual interest and a complete lack of any desire for intercourse the following night.

By contrast, when the same tests were carried out on three successive nights, using the same 3.1% gel mixture supplemented with 0.1 or 0.2 grams of zinc lactate each night, dissolved in a single drop of water and then mixed into the gel, there was no comparable feeling of lingering physical irritation after the third night. The male felt significantly more comfortable and pleasant.

These test results described in Examples 1 and 2 indicate that zinc lactate can effectively reduce the levels of both short-term and intermediate-term irritation caused by a spermicidal surfactant which is toxic to sperm cells and to various types of microbes.

EXAMPLE 3: REDUCTION OF SURFACTANT IRRITATION BY ZINC GLUCONATE

A gel mixture containing 3.1% nonoxynol was prepared as described in Example 2. It was tested on three successive nights, using about 0.5 grams (each time) of powdered zinc gluconate (purchased from Amend Chemical Company, in Irvington, New Jersey, USA). This preparation was predominately a relatively fine powder, with a relatively small quantity of larger granules in the powder. It was substantially more soluble in water than previously-tested granular formulations, and did not require any additional solubilizing steps or agents.

The resulting 3.1% gels were tested for irritation, on three successive nights. Each time, the male volunteer found that the level of irritation caused by the nonoxynol was substantially less annoying and distracting than from the 3.1% nonoxynol gel without any zinc. In addition, there was no feeling of lingering physical irritation in the genitals after the third night.

These test results indicate that zinc gluconate reduces both short-term and intermediate-term irritation caused by a spermicidal surfactant that is toxic to sperm cells and to various types of microbes.

EXAMPLE 4: ACIDITY TESTS AND ZINC SULFATE

In view of the fact that acidity is generated when highly ionizing zinc salts are dissolved in water, several zinc salts were tested to evaluate their effects on pH. All solutions were mixed at 5% w/v concentrations, by weighing out a quantity of the zinc salt into a small bottle, then pipetting a calculated quantity of distilled deionized water into the bottle to make up a 5% solution. The zinc lactate did not dissolve immediately, so it was immersed in a water bath at 70°C and occasionally shaken until the solution became clear. The pH of each solution was then measured.

The calibration setting on the pH meter was not working properly, and the meter could not be calibrated to 7.00 using a standard reference fluid; however, the reading remained steady at 7.05 in the neutral calibration fluid, so the readings were deemed to be approximately accurate, and a fixed value of 0.05 was subtracted from each meter reading, to provide the numbers reported below.

The zinc acetate solution (0.8073 g of dihydrate salt, formula weight 219.5, mixed with 13.5 ml water) had a pH of 6.27. The zinc lactate solution (0.2645 g of monohydrate hemi-zinc salt, formula weight 261.6 per mole of zinc, mixed with 4.925 ml water) had a pH of 6.16. The zinc sulfate solution (0.428 g of heptahydrate salt, formula weight 287.5, mixed with 6.755 ml water) had a pH of 5.58, which was substantially more acidic than either the zinc acetate or zinc lactate.

The 5% zinc sulfate solution described above was adjusted to a pH of about 6.8, by adding several drops of 1 N sodium hydroxide solution. A precipitate was formed, but generally resolved upon heating in a 70°C water bath. This semi-neutralized solution was mixed with an approximately 4 times greater volume of K-Y Lubricating Jelly, to provide a zinc sulfate gel containing about 1% w/v zinc sulfate. It was tested for irritation by human

volunteers, and caused no noticeable irritation.

Thus, there has been shown and described a new and useful method for reducing the irritation caused by spermicidal and/or microbicidal toxins in condom lubricants and other topical genital formulations used in connection with sexual intercourse, and for reducing the risk and severity of allergic reactions to latex condoms. Although this invention has been exemplified for purposes of illustration and description by reference to certain specific embodiments, it will be apparent to those skilled in the art that various modifications, alterations, and equivalents of the illustrated examples are possible. Any such changes which derive directly from the teachings herein, and which do not depart from the spirit and scope of the invention, are deemed to be covered by this invention.

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CLAIMS

1. A method for reducing irritation caused by a spermicidal or microbicidal toxin in a topical genital formulation, comprising the step of incorporating in the topical genital formulation at least one pharmaceutically acceptable zinc compound at a concentration which is effective in reducing irritation caused by the toxin.

2. The method of Claim 1 wherein the toxin comprises a spermicidal surfactant.

3. The method of Claim 2 wherein the spermicidal surfactant is selected from the group consisting of nonoxynol and octoxynol.

4. The method of Claim 1 wherein the toxin comprises a microbicide.

5. The method of Claim 4 wherein the zinc compound is selected from the group consisting of zinc acetate, zinc butyrate, zinc formate, zinc gallate, zinc gluconate, zinc glycerate, zinc glycolate, zinc lactate, zinc maleate, zinc malonate, zinc propionate, zinc pyruvate, zinc succinate, zinc chloride, and zinc sulfate.

6. The method of Claim 1 wherein the zinc compound is incorporated in a fluidized lubricant formulation at a concentration of about 0.03 percent to about 15 percent, on a weight per volume basis.

7. A method for preparing a topical genital formulation which contains a spermicidal or microbicidal toxin and which has a reduced tendency to cause irritation when topically applied to skin in connection with sexual intercourse, comprising the step of incorporating in the topical genital formulation at least one pharmaceutically acceptable zinc compound at a concentration which is effective in reducing irritation caused by the toxin.

8. The method of Claim 7 wherein the toxin comprises a spermicidal surfactant.

9. The method of Claim 8 wherein the spermicidal surfactant is selected from the group consisting of nonoxynol and octoxynol.

10. The method of Claim 7 wherein the toxin comprises a microbicide.

11. The method of Claim 7 wherein the zinc compound is selected from the group consisting of zinc acetate, zinc butyrate, zinc formate, zinc gallate, zinc gluconate, zinc glycerate, zinc glycolate, zinc lactate, zinc maleate, zinc malonate, zinc propionate, zinc pyruvate, zinc succinate, zinc chloride, and zinc sulfate.

12. The method of Claim 7 wherein the zinc compound is incorporated in a fluidized lubricant formulation at a concentration of about 0.03 percent to about 15 percent, on a

weight per volume basis.

13. A method for reducing irritation caused by a spermicidal or microbicidal toxin in a topical genital formulation, comprising the step of applying, to at least one skin surface, a topical genital formulation containing (i) a spermicidal or microbicidal toxin, and (ii) at least one pharmaceutically acceptable zinc compound at a concentration which is effective in reducing irritation caused by the toxin.

14. The method of Claim 13 wherein the toxin comprises a spermicidal surfactant.

15. The method of Claim 14 wherein the spermicidal surfactant is selected from the group consisting of nonoxynol and octoxynol.

16. The method of Claim 13 wherein the toxin comprises a microbicide.

17. The method of Claim 13 wherein the zinc compound is selected from the group consisting of zinc acetate, zinc butyrate, zinc formate, zinc gallate, zinc gluconate, zinc glycerate, zinc glycolate, zinc lactate, zinc maleate, zinc malonate, zinc propionate, zinc pyruvate, zinc succinate, zinc chloride, and zinc sulfate.

18. The method of Claim 13 wherein the zinc compound is incorporated in a fluidized lubricant formulation at a concentration of about 0.03 percent to about 15 percent, on a weight per volume basis.

19. A topical genital formulation for use in connection with sexual intercourse, comprising:

a. at least one spermicidal or microbicidal toxin, at a concentration which renders the topical formulation effective as a spermicide or microbicide;

b. at least one pharmaceutically acceptable zinc compound, at a concentration which is effective in reducing irritation caused by the toxin; and,

c. a carrier substance which renders the topical formulation suitable for repeated use during numerous acts of sexual intercourse.

20. The topical genital formulation of Claim 19, wherein the carrier substance renders the topical formulation useful as a lubricant for packaging with a condom.

21. The topical genital formulation of Claim 20, wherein the zinc compound is selected from the group consisting of zinc acetate, zinc butyrate, zinc formate, zinc gallate, zinc gluconate, zinc glycerate, zinc glycolate, zinc lactate, zinc maleate, zinc malonate, zinc propionate, zinc pyruvate, zinc succinate, zinc chloride, and zinc sulfate.

22. The topical genital formulation of Claim 19, wherein the carrier substance comprises an aqueous gel.

23. The topical genital formulation of Claim 22, wherein the zinc compound is selected from the group consisting of zinc acetate, zinc butyrate, zinc formate, zinc gallate, zinc gluconate, zinc glycerate, zinc glycolate, zinc lactate, zinc maleate, zinc malonate, zinc propionate, zinc pyruvate, zinc succinate, zinc chloride, and zinc sulfate.

24. The topical genital formulation of Claim 19, wherein the carrier substance renders the topical formulation useful for insertion deep inside a vagina, prior to intercourse.

25. The topical genital formulation of Claim 24, wherein the zinc compound is selected from the group consisting of zinc acetate, zinc butyrate, zinc formate, zinc gallate, zinc gluconate, zinc glycerate, zinc glycolate, zinc lactate, zinc maleate, zinc malonate, zinc propionate, zinc pyruvate, zinc succinate, zinc chloride, and zinc sulfate.

26. An article of manufacture comprising a condom, a fluidized condom lubricant, and a watertight package containing the condom and the fluidized condom lubricant, wherein the fluidized condom lubricant contains:

a. at least one spermicidal or microbicidal toxin, at a concentration which renders the fluidized condom lubricant effective as a spermicide or microbicide;

b. at least one pharmaceutically acceptable zinc compound, at a concentration which is effective in reducing irritation caused by the toxin; and,

c. a carrier substance which renders the fluidized condom lubricant suitable for repeated use during numerous acts of sexual intercourse.

27. The article of manufacture of Claim 26, wherein the zinc compound is selected from the group consisting of zinc acetate, zinc butyrate, zinc formate, zinc gallate, zinc gluconate, zinc glycerate, zinc glycolate, zinc lactate, zinc maleate, zinc malonate, zinc propionate, zinc pyruvate, zinc succinate, zinc chloride, and zinc sulfate.

28. The article of manufacture of Claim 26 wherein the zinc compound is incorporated in the fluidized lubricant formulation at a concentration of about 0.03 percent to about 15 percent, on a weight per volume basis.

29. An article of manufacture, comprising an aqueous gel and a watertight package containing the aqueous gel, wherein the aqueous gel is designed for use as a topical genital formulation and contains:

a. an aqueous carrier substance;

b. at least one spermicidal or microbicidal toxin, at a concentration which renders the aqueous gel effective as a spermicide or microbicide; and,

c. at least one pharmaceutically acceptable zinc compound, at a concentration which is effective in reducing irritation caused by the toxin.

30. The article of manufacture of Claim 29, wherein the watertight package comprises a tube which is sealed at a first end and which is provided with a closable orifice at a second opposed end.

31. The article of manufacture of Claim 30, wherein the zinc compound is selected from the group consisting of zinc acetate, zinc butyrate, zinc formate, zinc gallate, zinc gluconate, zinc glycerate, zinc glycolate, zinc lactate, zinc maleate, zinc malonate, zinc propionate, zinc pyruvate, zinc succinate, zinc chloride, and zinc sulfate.

32. The article of manufacture of Claim 29, wherein the watertight package comprises a sealed disposable plastic packet containing a quantity of gel intended for use during a single act of intercourse.

33. The article of manufacture of Claim 32, wherein the zinc compound is selected from the group consisting of zinc acetate, zinc butyrate, zinc formate, zinc gallate, zinc gluconate, zinc glycerate, zinc glycolate, zinc lactate, zinc maleate, zinc malonate, zinc propionate, zinc pyruvate, zinc succinate, zinc chloride, and zinc sulfate.

34. An article of manufacture, comprising a sealed packaging enclosure which encloses:

a. at least one vaginal applicator designed for inserting a fluidized substance into a vagina; and,

b. at least one quantity of a fluidized topical genital formulation which is intended for insertion into a vagina prior to intercourse, which comprises:

(i) at least one spermicidal or microbicidal toxin, at a concentration which renders the fluidized substance effective as a spermicide or microbicide;

(ii) at least one pharmaceutically acceptable zinc compound, at a concentration which is effective in reducing irritation caused by the toxin; and

(iii) a carrier substance which renders the topical formulation suitable for repeated use during numerous acts of sexual intercourse.

35. The article of manufacture of Claim 34, wherein the zinc compound is selected from the group consisting of zinc acetate, zinc butyrate, zinc formate, zinc gallate, zinc gluconate, zinc glycerate, zinc glycolate, zinc lactate, zinc maleate, zinc malonate, zinc propionate, zinc pyruvate, zinc succinate, zinc chloride, and zinc sulfate.

36. The article of manufacture of Claim 34 wherein the zinc compound is

incorporated in the fluidized topical formulation at a concentration of about 0.03 percent to about 15 percent, on a weight per volume basis.

37. A method for reducing adverse physical reactions to latex condoms, comprising the step of incorporating in a condom lubricant at least one pharmaceutically acceptable zinc compound at a concentration which is effective in reducing adverse physical reactions to latex condoms when the condom lubricant containing the zinc compound is applied topically to skin.

38. The method of claim 37, wherein the adverse physical reaction is selected from the group consisting of short-term irritation, intermediate-term irritation, long-term irritation, and skin inflammation.

39. The method of claim 37, wherein the adverse physical reaction is selected from the group consisting of an allergic reaction to latex, and hypersensitization of a condom user's immune system to latex proteins.

40. The method of Claim 39, wherein the zinc compound is selected from the group consisting of zinc acetate, zinc butyrate, zinc formate, zinc gallate, zinc gluconate, zinc glycerate, zinc glycolate, zinc lactate, zinc maleate, zinc malonate, zinc propionate, zinc pyruvate, zinc succinate, zinc chloride, and zinc sulfate.

41. The method of Claim 39, wherein the zinc compound is incorporated in the condom lubricant at a concentration of about 0.03 percent to about 30 percent, on a weight per volume basis.

42. A method of preparing a condom lubricant which reduces allergic reactions to latex condoms, comprising the step of incorporating in the condom lubricant at least one pharmaceutically acceptable zinc compound at a concentration which is effective in reducing allergic reactions to latex condoms when the condom lubricant containing the zinc compound is applied topically to skin.

43. A method for reducing allergic reactions to latex condoms, comprising the step of coating a latex condom with a suitable condom coating formulation containing at least one pharmaceutically acceptable zinc compound in a concentration which is effective in reducing allergic reactions to latex condoms when the condom coating formulation containing the zinc compound is applied topically to skin.

44. A method for reducing allergic reactions to latex condoms, comprising the step of applying to at least one skin surface a condom lubricant containing at least one pharmaceutically acceptable zinc compound at a concentration which is effective in reducing

allergic reactions to latex condoms when the condom lubricant containing the zinc compound is applied topically to skin.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 402 078 A (KELLY) 12 December 1990 see column 12, line 44 - column 13, line 6 see claims 1-18 & US 5 624 675 A cited in the application ---	1-28, 34-44
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Y	EP 0 564 307 A (LEVI ET AL) 6 October 1993 see abstract see examples 6,13 see claims 1,5,7,12 --- -/--	1-25

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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